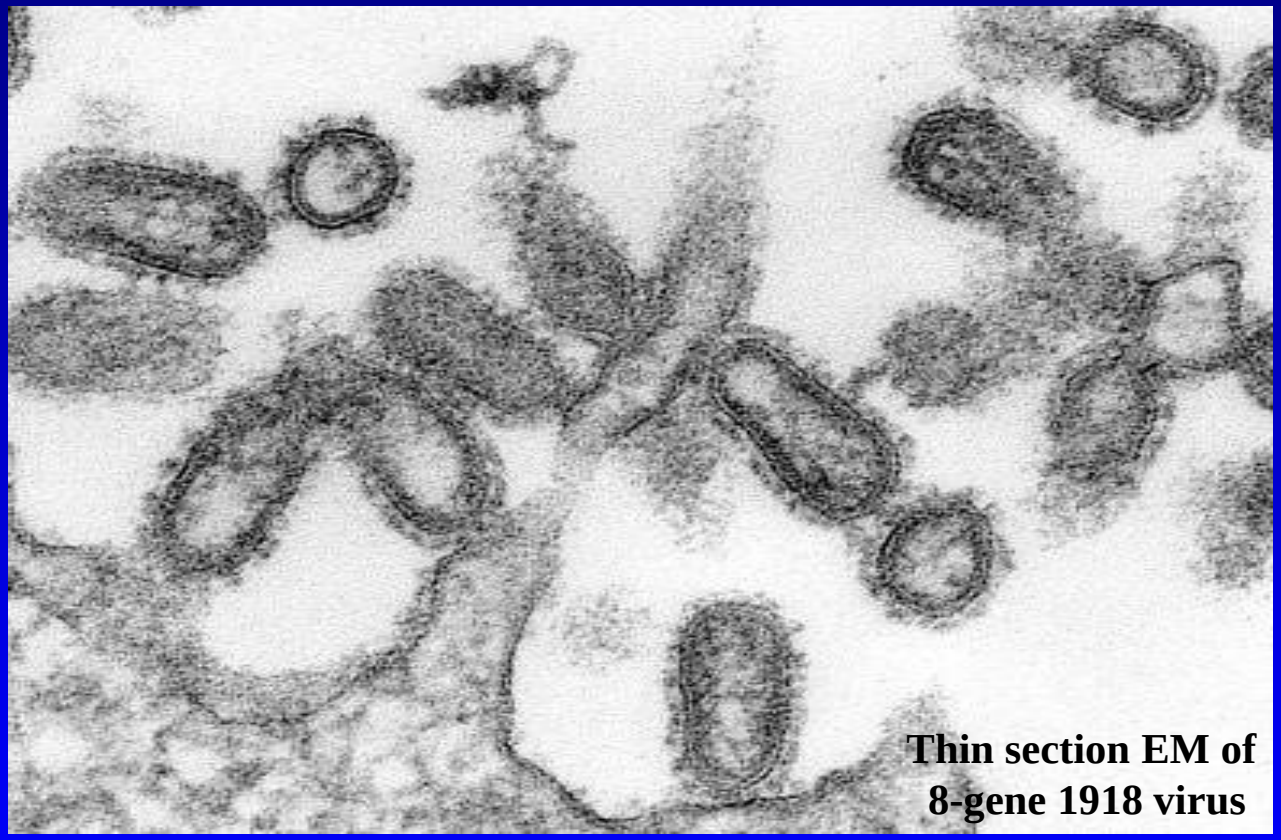
Resurrection of the 1918 Influenza: What Did We Learn?



Thin section EM of 8-gene 1918 virus

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Rationale for 1918 project

- Naturally occurring pandemic but no direct information on pandemic virus available (no viral isolates from 1918)

- Data from virus would have important biomedical and epidemiological implications to mitigate future pandemics;

  - How did the pandemic virus evolve and adapt to humans? Can we identify mutations to be used for surveillance?

  - Why was it so pathogenic, especially in young adults? Could data be used to develop novel therapeutics and vaccines?

The 1918 virus was handled safely in enhanced BSL3 conditions with additional CDC lab operating procedures

Primary Barrier
(BSC)

Secondary Barrier
(PAPR)

Enhanced CDC laboratory operating procedures for work with the 1918 influenza virus

- All personnel working with 1918 adhere to the standard BSL3+ PPE, including PAPRs, double gloves, scrubs, shoe covers, surgical gowns and personal showers prior to exiting the laboratory.

- All animal infections and other manipulations with this agent should be performed in a certified Class II biosafety cabinet (BSC). Only this agent should be worked on in a BSC at any given time.

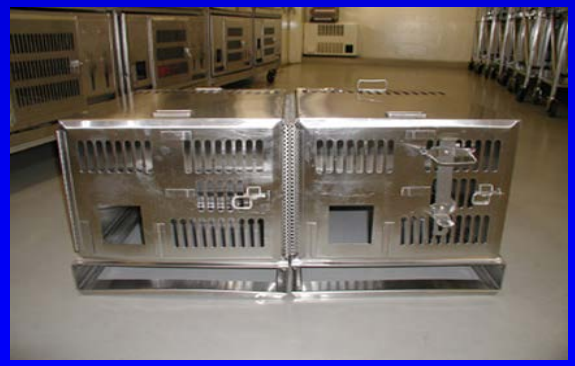
- It is required that all personnel working with the 1918 virus use influenza antiviral prophylaxis. The prophylactic dose of oseltamivir (Tamiflu) treatment is 1 capsule/day-75 mg. Tamiflu should be taken two days prior to and 10 days after 1918 virus work.

CDC

Enhanced CDC laboratory operating procedures for work with the 1918 influenza virus –Cont.

- **Participating ABSL3 staff, including the attending veterinarian (AV), ABSL3 manager and animal caretakers must receive a biosafety briefing and experimental background that reinforces awareness of potential occupational hazards of working with this agent.**

- **Any personnel not taking antiviral prophylaxis will not be admitted into the individual animal room or bioclean unit (bioisolator) containing 1918 infected animals. However, the AV should have access in the event of an emergency.**

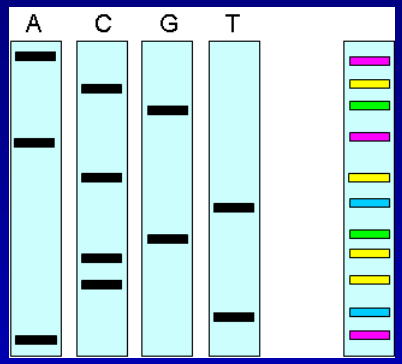


Ferret caging

Bioisolator (negative pressure)

Reconstruction of the 1918 influenza virus

Lung tissues from 1918 pandemic victims



Gene sequencing

Gene reconstruction

Virus rescue

Infectious 1918 virus in BSL-3 enhanced lab CDC Atlanta

Use the 1918 virus as a model for pandemic influenza

Main Objectives

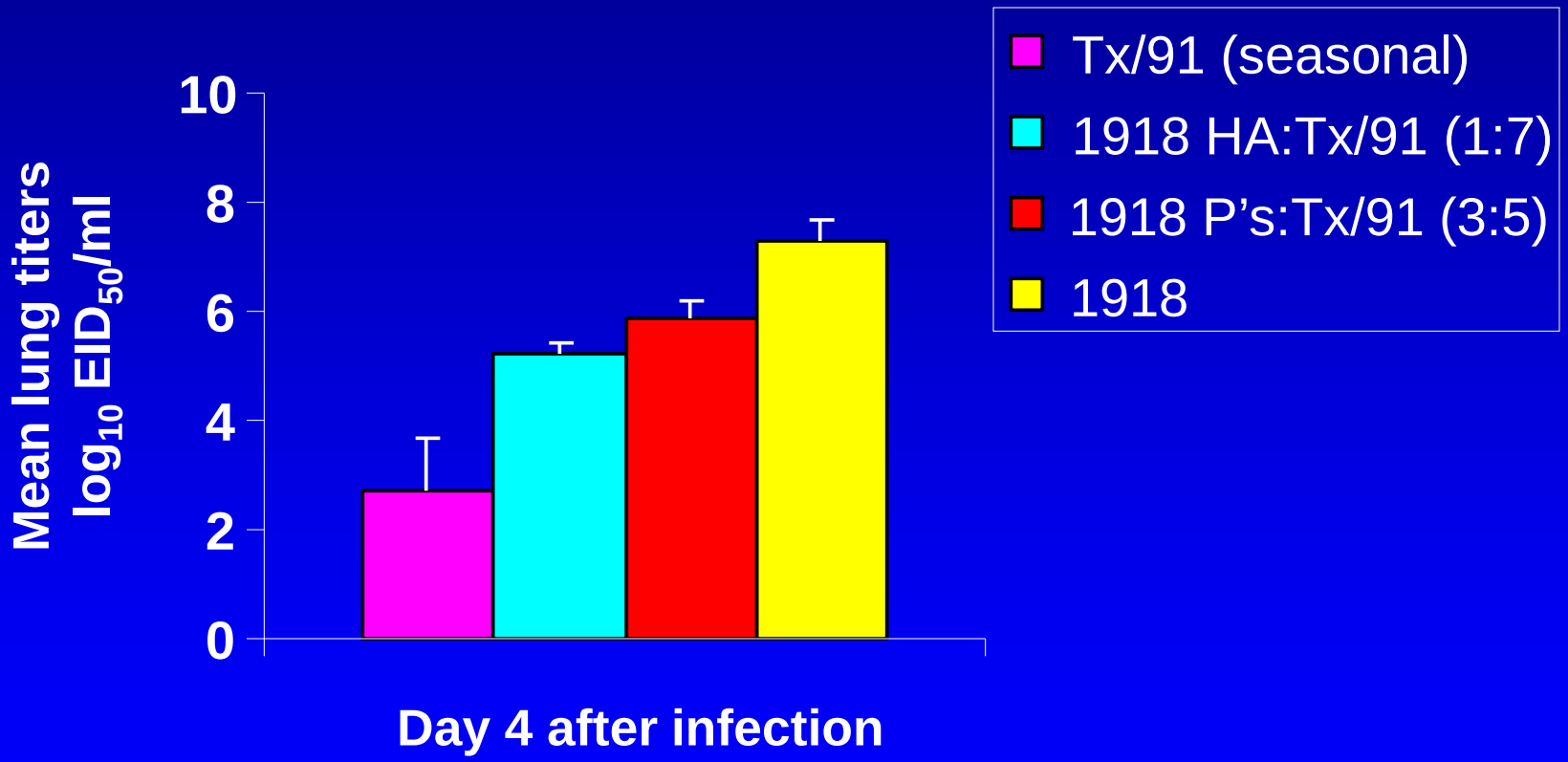
1. Identify properties that are responsible for the extraordinary virulence of the 1918 influenza virus

2. Identify genetic determinants responsible for the transmissibility of this pandemic virus

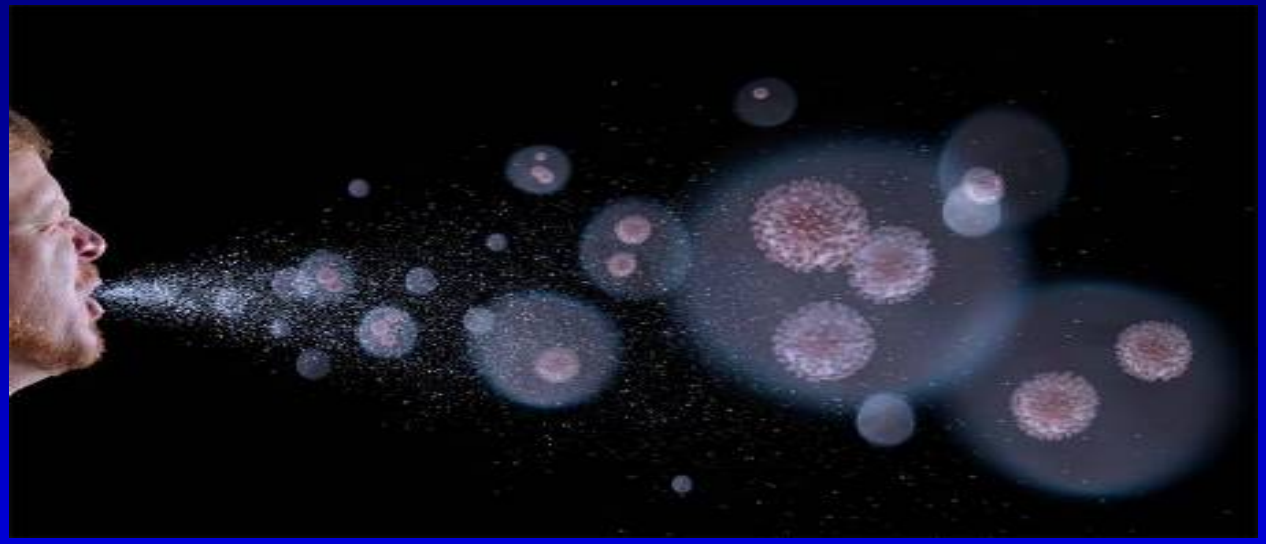
3. Assess vaccine efficacy against a naturally occurring pandemic virus.

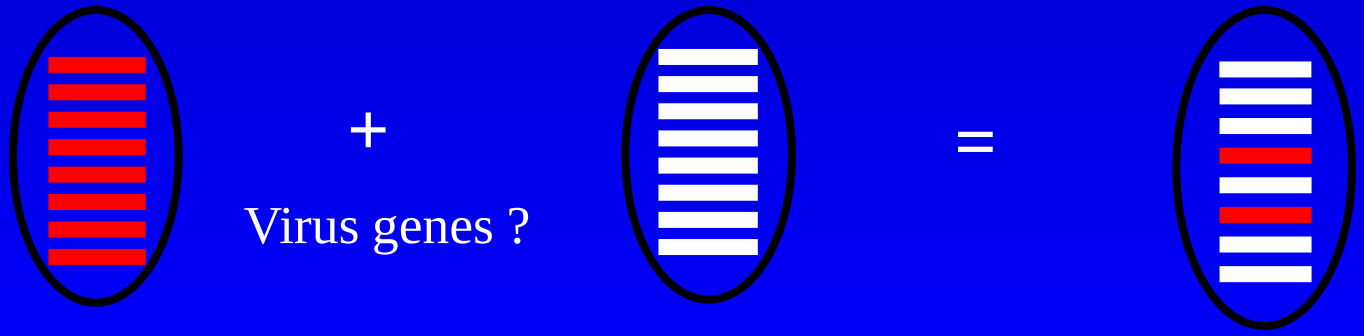
CDC

1918 HA and polymerase (P's) genes are essential optimal virulence and replication in mouse lungs



What 1918 virus genes confer efficient transmission?





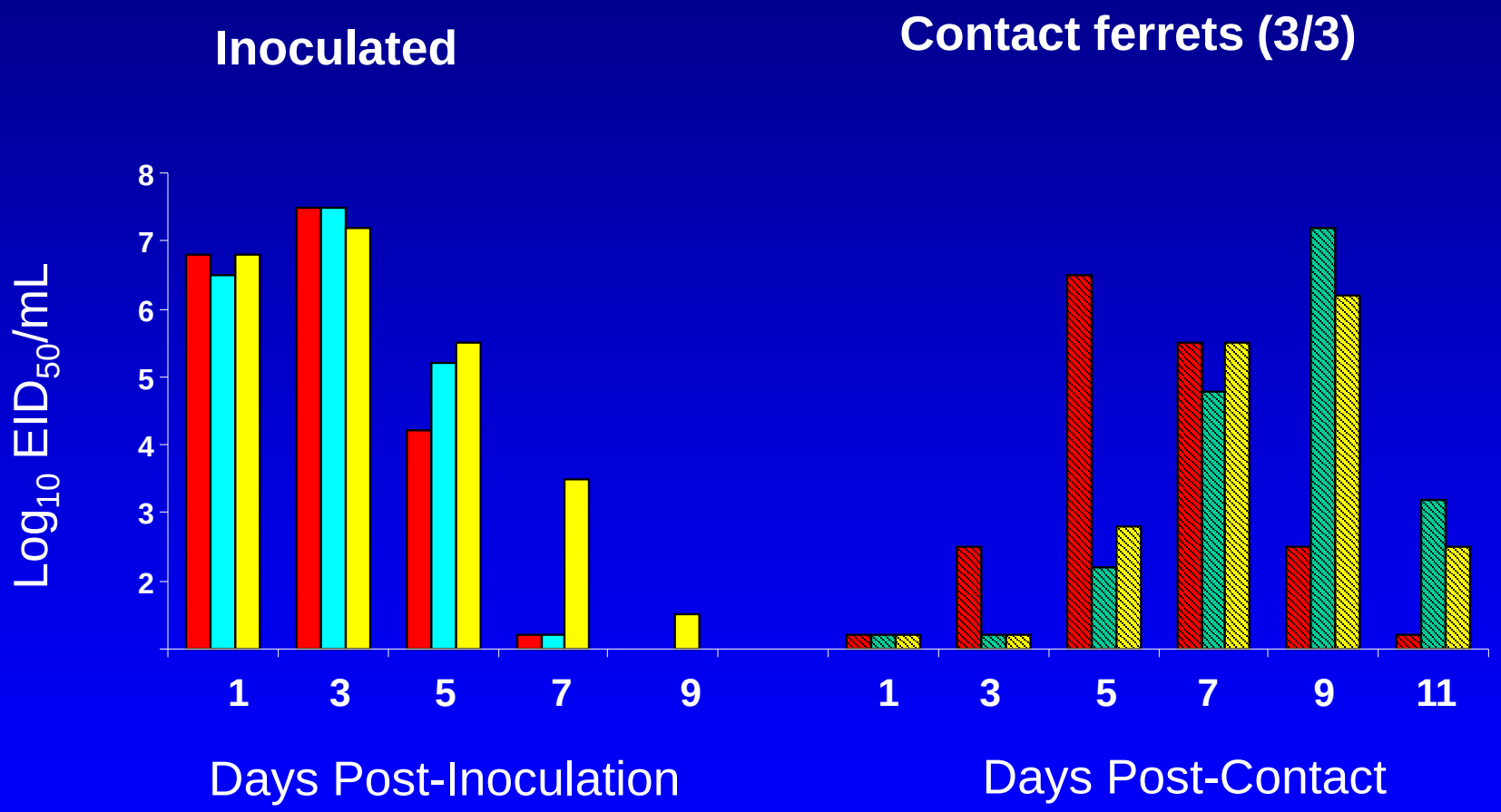
Human H1N1 (1918)

Avian H1N1 (Duck/NY/96)

Efficient Transmission

CDC

Transmission of 1918 HAPB2:Dk/NY/96 virus



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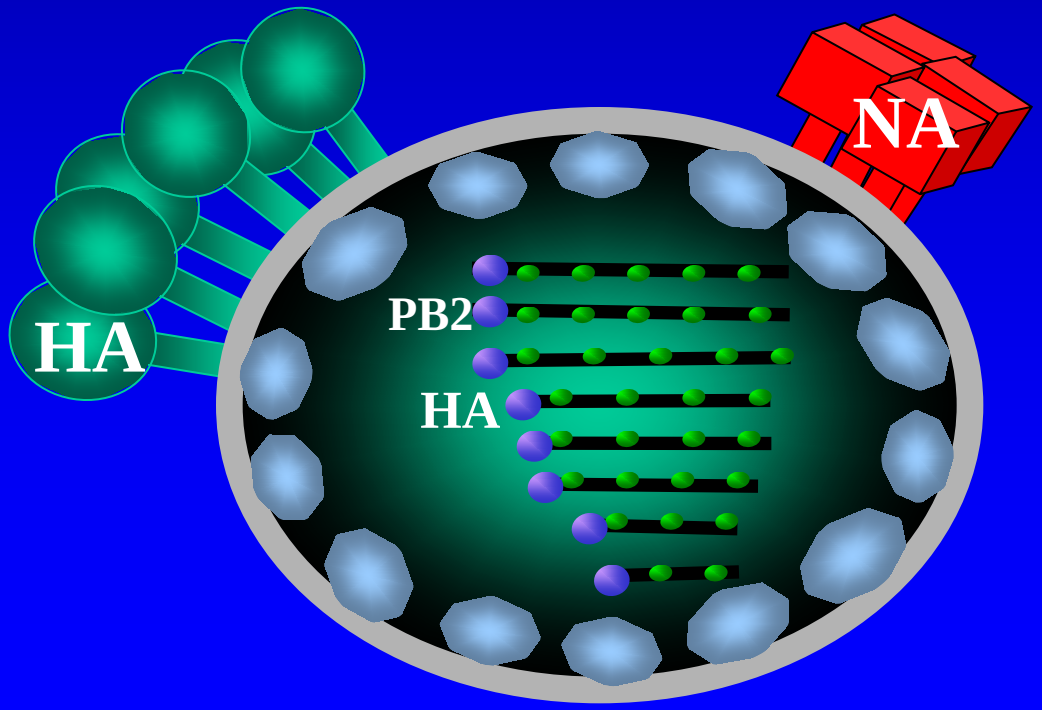
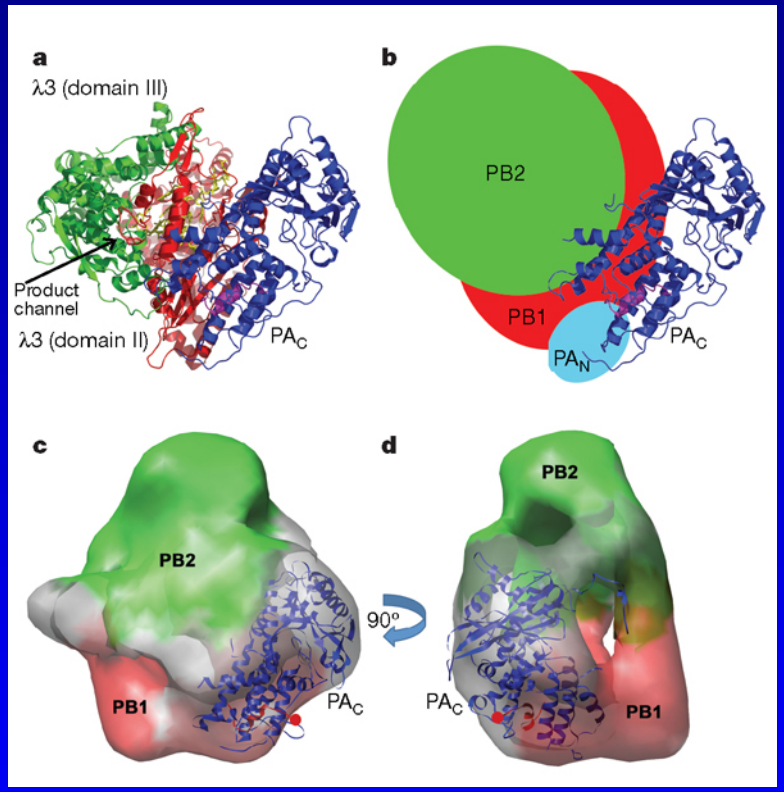
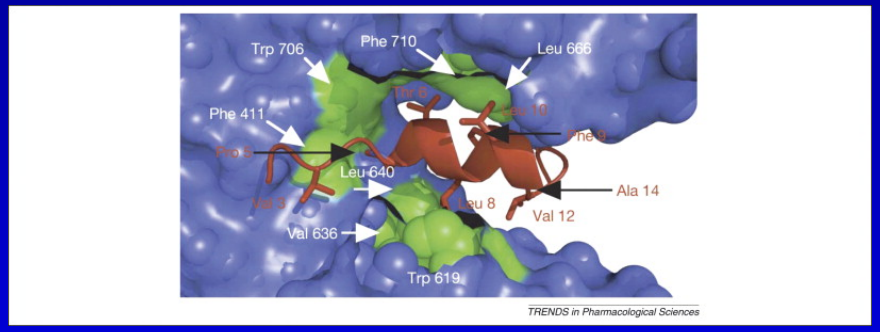
The research findings suggest that "human" adaptation of the HA and PB2 proteins of H1N1 avian influenza viruses are required to generate viruses readily transmissible through the air



CDC

Potential antiviral target in the viral polymerase

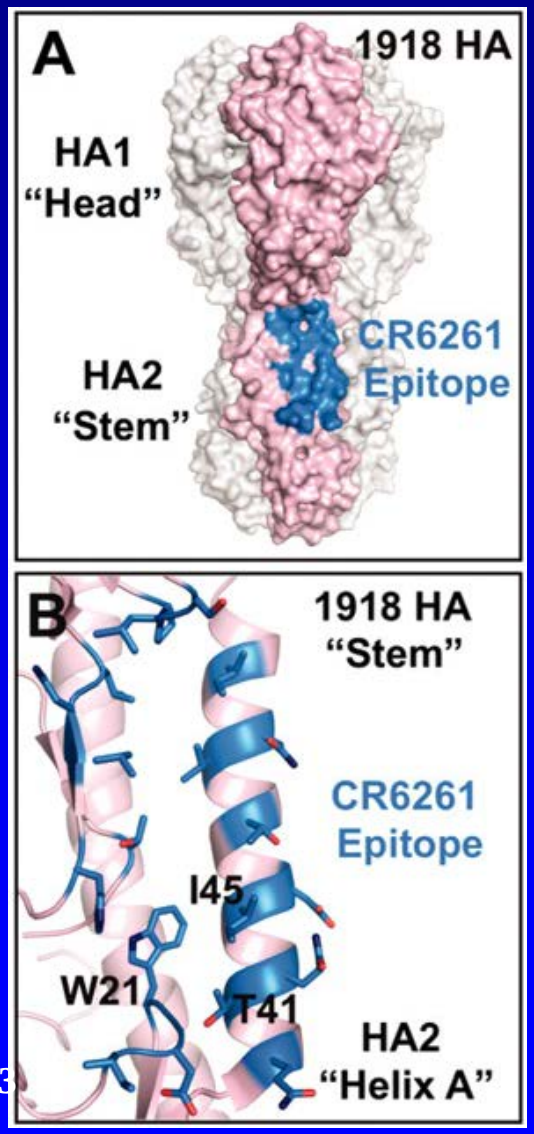


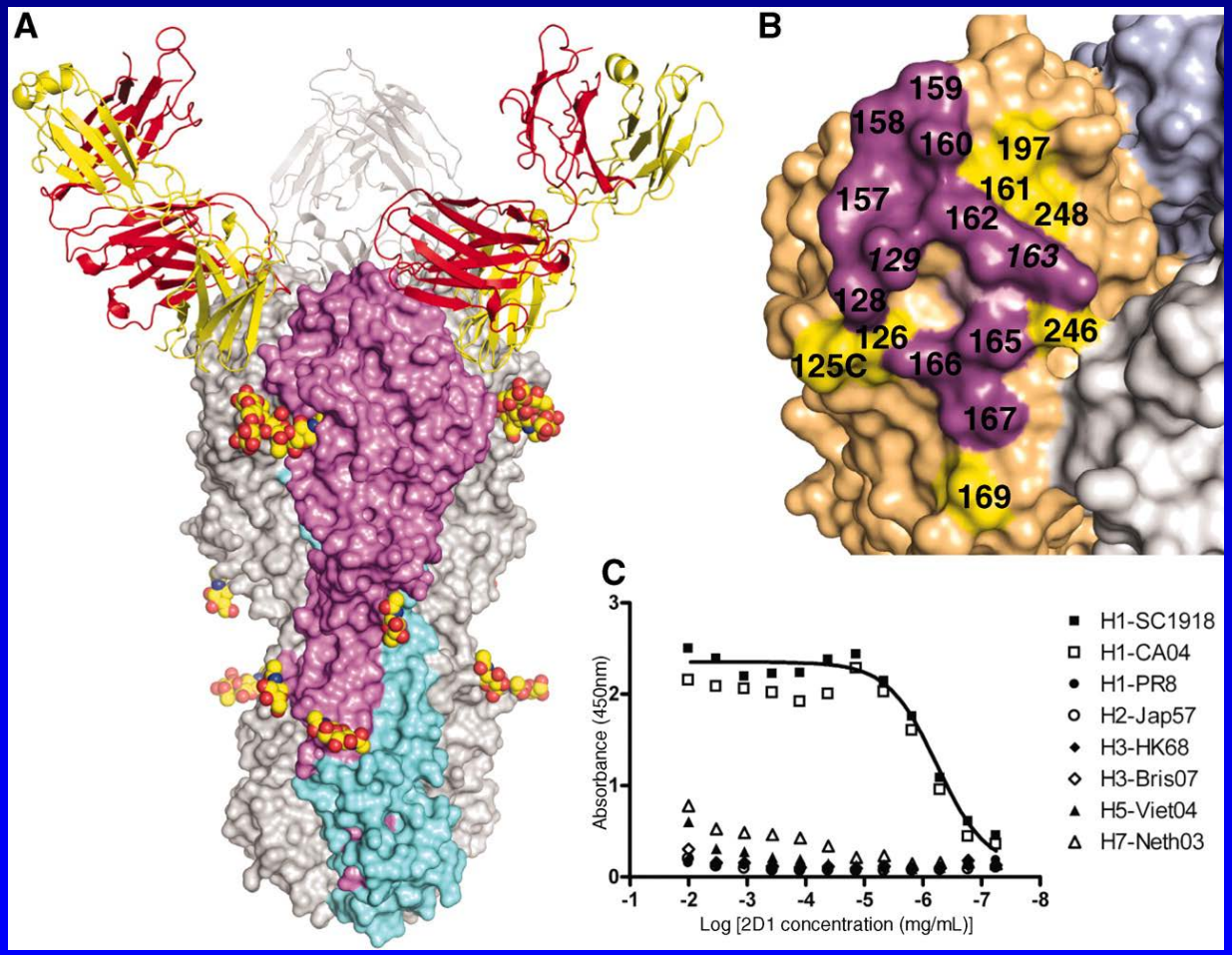


Ghanem *et al.* J Virol. 2007 81:7801–7804.

Fleishman *et al*. PNAS 2012 109:6247-52

Use of 1918 HA structure to develop monoclonals & broadly reactive vaccines

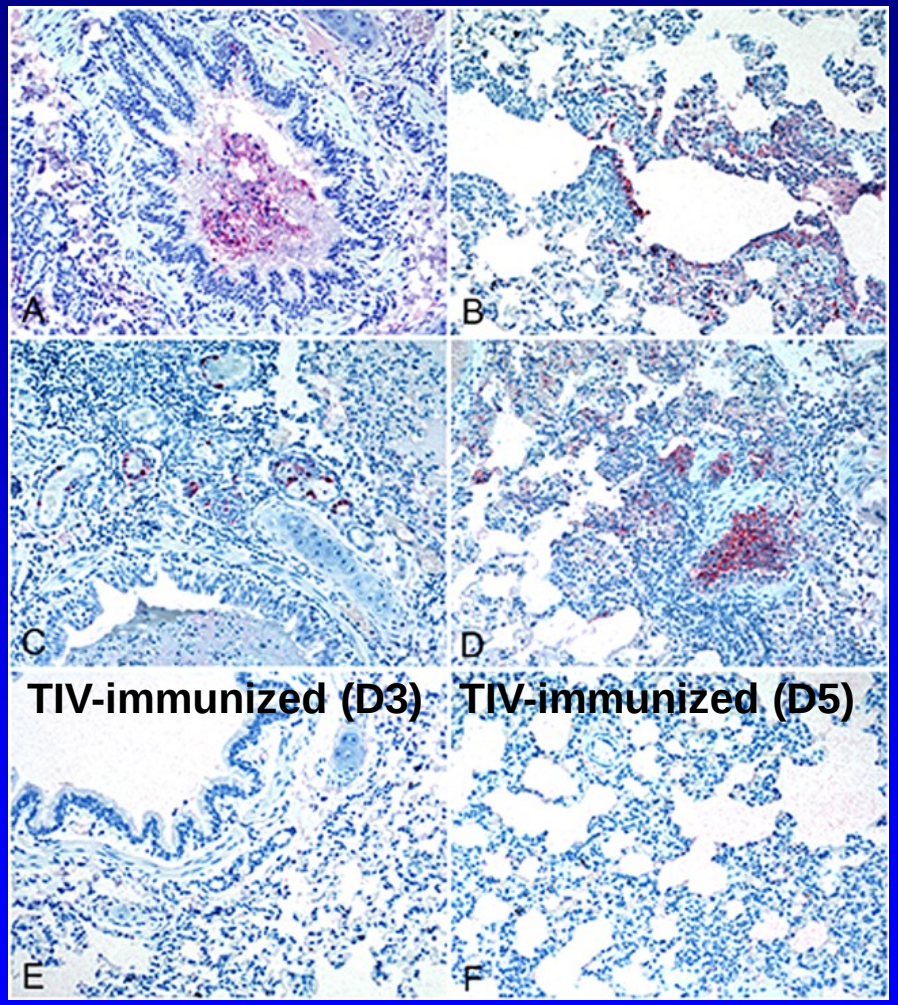




Xu *et al.* 2010 Science 328:357

Fleishman *et al*. 2011 Science 332:816

Seasonal trivalent inactivated influenza vaccine protects against 1918 Spanish influenza virus infection in ferrets



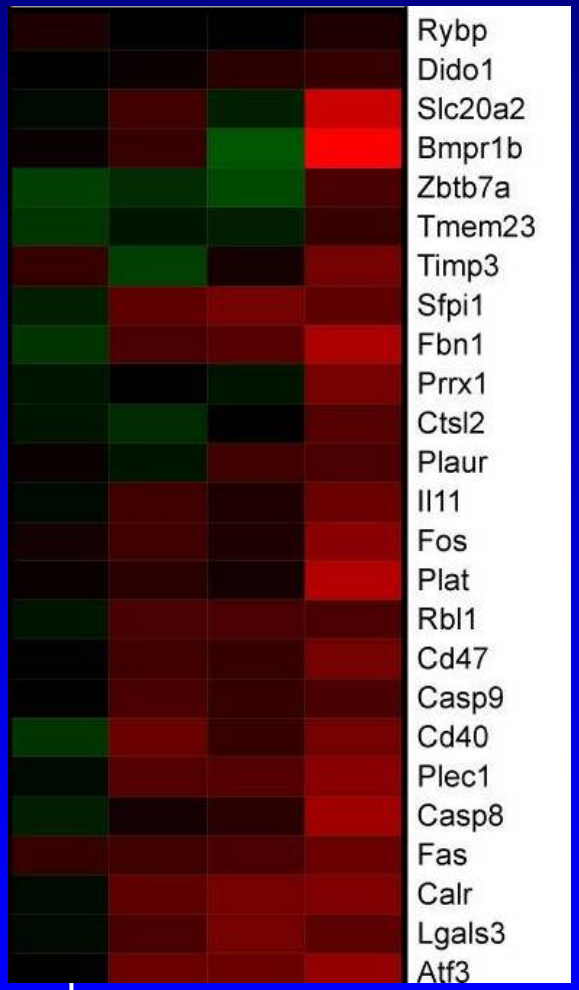
- Lung tissue sections from control (A to D) and TIV-immunized (E and F) ferrets

- Stained (in red) for the presence of viral antigen 3 and 5 days p.c.

Pearce *et al*. 2012 J Virol. 86:7118

CDC

Up-regulated inflammatory responses during 1918 virus infection

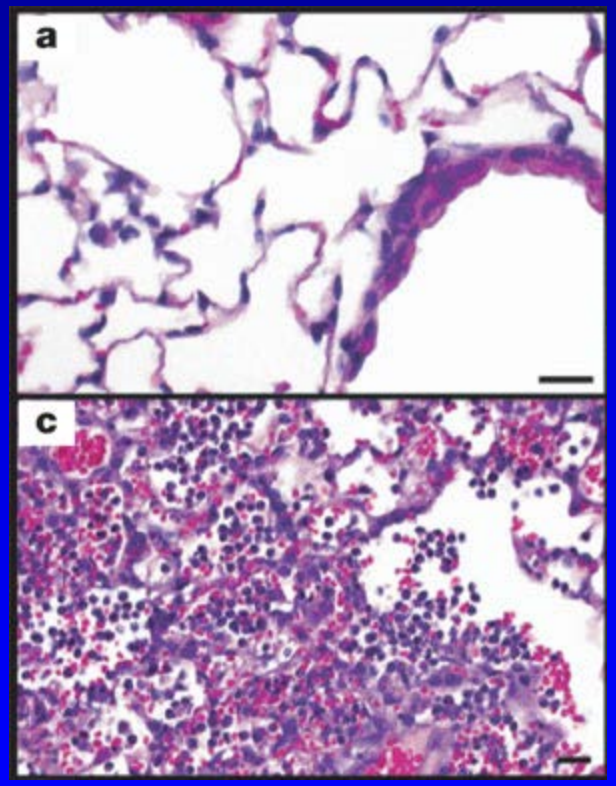


Seasonal H1N1

(sH1N1)

1918

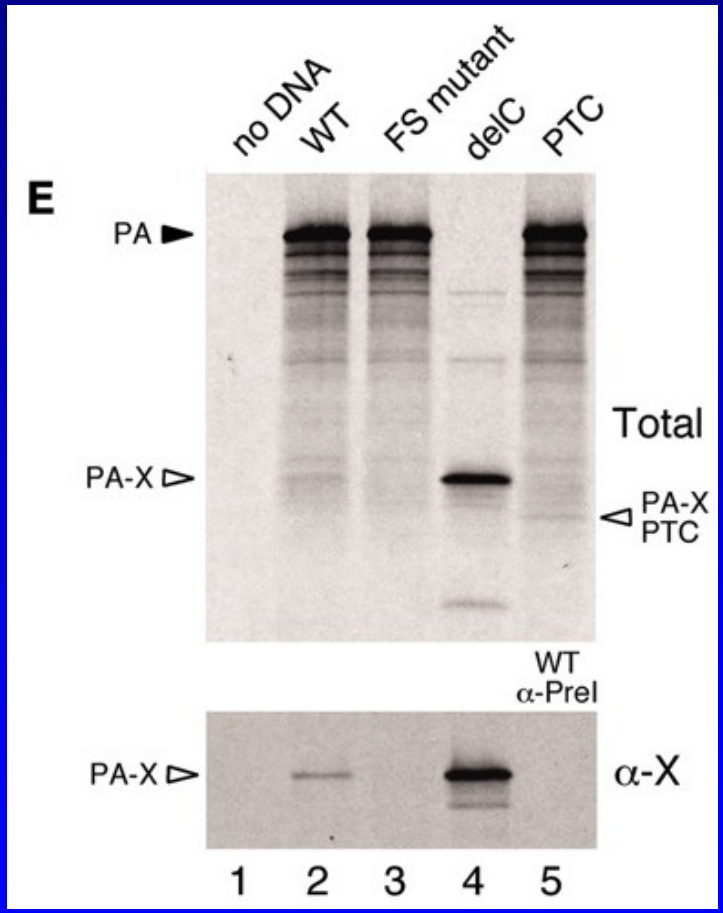
Infected mouse lungs



Kash *et al.* 2006 *Nature* 443:578

1918 virus genome used to identify a novel influenza protein

- Novel ORF encoded by influenza A virus
- Encodes a non-structural protein that alters the host inflammatory response, including down-regulation of MHC class I genes
- Novel target for therapeutics development and for vaccine effectiveness



Jagger *et al.* 2012 Science 337:199

Conclusions

- The 1918 virus sequence has been utilized in hundreds of published studies.

- Resurrection of the 1918 influenza virus has significantly enhanced our understanding of influenza pathobiology and identified novel targets for antiviral therapies.

Acknowledgements

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